

What is claimed is:

1. A model of an Fc receptor (FcR) protein, wherein said model represents a three dimensional structure that substantially conforms to the atomic coordinates of Table 1.

2. The model of Claim 1, wherein said structure substantially conforms to the atomic coordinates and B-values represented by Table 1.

3. The model of Claim 1, wherein said structure is monomeric.

4. The model of Claim 1, wherein said structure is dimeric.

5. The model of Claim 1, wherein said structure substantially conforms to the atomic coordinates of a table selected from the group consisting of Table 2, Table 3, Table 4 and Table 5.

6. The model of Claim 1, wherein at least about 50% of said structure has an average root-mean-square deviation (RMSD) of less than about 1.5Å for backbone atoms in secondary structure elements in each domain of said structure.

7. The model of Claim 1, wherein at least about 50% of common amino acid side chains between said structure and a structure comprising said atomic coordinates have an average root-mean-square deviation (RMSD) of less than about 1.5Å.

8. The model of Claim 1, wherein said FcR protein comprises an amino acid sequence that is at least about 25% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:10, SEQ ID NO:11 and SEQ ID NO:12.

9. The model of Claim 1, wherein said FcR protein comprises an amino acid sequence that is at least about 40% identical to an amino acid sequence selected from the group

5 consisting of SEQ ID NO:3, SEQ ID NO:10, SEQ ID NO:11 and SEQ ID NO:12.

10. The model of Claim 1, wherein said FcR protein comprises an amino acid sequence that is at least about 60% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:10, SEQ ID NO:11 and SEQ 5 ID NO:12.

11. The model of Claim 1, wherein said FcR protein comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, a mutant of any of said amino acid sequences, and an allelic variant of any of said amino acid sequences.

12. The model of Claim 1, wherein said FcR protein comprises an amino acid sequence selected from the group consisting of: an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13; a mutant of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12 or SEQ ID NO:13; and an allelic variant of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ 10 ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12 or SEQ ID NO:13.

13. The model of Claim 1, wherein said FcR protein is selected from the group consisting of Fc γ RI protein, Fc γ RIIa protein, Fc γ RIIb protein, Fc γ RIIc protein, Fc γ RIII protein, Fc ϵ RI protein, Fc α RI protein and structural homologues of any 5 of said FcR proteins.

14. The model of Claim 1, wherein said FcR protein is selected from the group consisting of Fc γ RI protein, Fc γ RIIa

protein, Fc γ RIIb protein, Fc γ RIIc protein, Fc γ RIII protein, Fc ϵ RI protein and Fc α RI protein.

15. The model of Claim 1, wherein said FcR protein is selected from the group consisting of an Fc γ RIIa protein monomer, an Fc γ RIIa protein dimer and structural homologues of said Fc γ RIIa proteins.

16. The model of Claim 1, wherein said FcR protein is selected from the group consisting of an Fc ϵ RI protein dimer, an Fc ϵ RI protein monomer and structural homologues of said Fc ϵ RI proteins.

17. The model of Claim 1, wherein said FcR protein is selected from the group consisting of an Fc γ RI protein dimer, an Fc γ RI protein monomer and structural homologues of said Fc γ RI protein.

18. The model of Claim 1, wherein said FcR protein is selected from the group consisting of an Fc γ RIIb protein dimer, an Fc γ RIIb protein monomer and structural homologues of said Fc γ RIIb protein.

19. The model of Claim 1, wherein said FcR protein is selected from the group consisting of an Fc γ RIIc protein dimer, an Fc γ RIIc protein monomer and structural homologues of said Fc γ RIIc protein.

20. The model of Claim 1, wherein said FcR protein is selected from the group consisting of an Fc γ RIIIb protein dimer, an Fc γ RIIIb protein monomer and structural homologues of said Fc γ RIIIb protein.

21. The model of Claim 1, wherein said FcR protein is selected from the group consisting of an Fc α RI protein dimer, an Fc α RI protein monomer and structural homologues of said Fc α RI protein.

22. The model of Claim 1, wherein said atomic coordinates are generated by the method comprising:

5 (a) providing an Fc γ RIIa protein in crystalline form;

5 (b) generating an electron-density map of said crystalline Fc γ RIIa protein; and

(c) analyzing said electron-density map to produce said atomic coordinates.

23. The model of Claim 22, wherein said crystalline Fc γ RIIa protein is produced by a method comprising: combining Fc γ RIIa protein with a mother liquor buffer selected from the group consisting of an acetate salt buffer and a sulphate buffer, and inducing crystal formation to produce said crystalline Fc γ RIIa protein.

24. The model of Claim 23, wherein said acetate buffer comprises about 200 mM ammonium acetate, about 100 mM sodium citrate and about 30% PEG 4000, said buffer having a pH of about 5.6.

25. The model of Claim 23, wherein said sulphate buffer comprises about 0.1 M HEPES and about 1.5 M lithium sulphate, said buffer having a pH of about 7.5.

26. The model of Claim 22, wherein said step of generating an electron-density map comprises analyzing said crystalline Fc γ RIIa protein by X-ray diffraction.

27. The model of Claim 22, wherein said crystalline Fc γ RIIa protein is derivatized in Di- γ -iodo bis{ethylenediamine} di Platinum(II) nitrate prior to said X-ray diffraction.

28. The model of Claim 22, wherein said crystalline Fc γ RIIa protein is derivatized in about 5 mM Di- γ -iodo bis[ethylenediamine] di Platinum(II) nitrate prior to said X-ray diffraction.

29. The model of Claim 1, wherein said model is a computer image generated by a computer-readable medium encoded

with a set of three dimensional coordinates of said three dimensional structure, wherein, using a graphical display software program, said three dimensional coordinates create an electronic file that can be visualized on a computer capable of representing said electronic file as a three dimensional image.

30. A computer-assisted method of structure based drug design of bioactive compounds, comprising:

a. providing a model of an Fc receptor (FcR) protein, wherein said model represents a three dimensional structure that substantially conforms to the atomic coordinates of Table 1;

- b. designing a chemical compound using said model; and,
- c. chemically synthesizing said chemical compound.

31. The method of Claim 30, wherein said method further comprises:

d. evaluating the bioactivity of said synthesized chemical compound.

32. The method of Claim 30, wherein said three dimensional structure comprises the atomic coordinates listed in Table 1.

33. The method of Claim 30, wherein said three dimensional structure is dimeric.

34. The method of Claim 30, wherein said three dimensional structure comprises the atomic coordinates listed in a table selected from the group consisting of Table 2, Table 3, Table 4, and Table 5.

35. The method of Claim 30, wherein said model comprises a computer image generated when the atomic coordinates listed in Table 1 are analyzed on a computer using a graphical display software program to create an electronic file of said image and visualizing said electronic file on a computer capable of representing said electronic file as a three dimensional image.

36. The method of Claim 30, wherein said step of designing comprises computational screening of one or more databases of chemical compounds in which the three dimensional structure of said compounds are known.

37. The method of Claim 36, further comprising interacting a compound identified by said screening step with said model by computer.

38. The method of Claim 30, wherein said step of designing comprises directed drug design.

39. The method of Claim 30, wherein said step of designing comprises random drug design.

40. The method of Claim 30, wherein said step of designing comprises grid-based drug design.

41. The method of Claim 30, wherein said step of designing comprises selecting compounds which are predicted to mimic said three dimensional structure of said FcR protein.

42. The method of Claim 30, wherein said step of designing comprises selecting compounds which are predicted to bind to said three dimensional structure of said FcR protein.

43. The method of Claim 30, wherein said bioactivity is selected from the group consisting of inhibiting binding of said FcR protein to an immunoglobulin protein, binding to said FcR protein, binding to an immunoglobulin which is capable of binding to said FcR protein, inhibiting phagocytosis of said immunoglobulin protein, inhibiting dimerization of said FcR protein, stimulating cellular signal transduction though said FcR protein, and stimulating release of cytokines through said FcR protein.

44. The method of Claim 30, wherein said FcR protein is Fc γ RIIa and said bioactivity is selected from the group consisting of inhibiting binding of Fc γ RIIa protein to IgG, inhibiting phagocytosis of IgG, inhibiting dimerization of Fc γ RIIa protein, stimulating cellular signal transduction though an Fc γ RIIa protein, stimulating release of cytokines selected from the group consisting of IL-6 and IL-12.

45. The method of Claim 30, wherein said FcR protein is Fc γ RIIb and said bioactivity is selected from the group consisting of inhibiting binding of Fc γ RIIb protein to IgG, inhibiting phagocytosis of IgG, inhibiting dimerization of Fc γ RIIb protein, stimulating cellular signal transduction through an Fc γ RIIb protein, stimulating release of cytokines selected from the group consisting of IL-6 and IL-12.

5 46. The method of Claim 30, wherein said FcR protein is Fc ϵ RI and said bioactivity is selected from the group consisting of inhibiting binding of Fc ϵ RI protein to IgE, inhibiting phagocytosis of IgE, inhibiting dimerization of Fc ϵ RI protein, stimulating cellular signal transduction through an Fc ϵ RI protein, stimulating release of histamine and serotonin by mast cells and inhibiting release of histamine and serotonin by mast cells.

47. A computer-assisted method of structure based drug design of bioactive compounds, comprising:

a. providing a model of an Fc receptor (FcR) protein, wherein said model represents a three dimensional structure that substantially conforms to the atomic coordinates selected from the group consisting of atomic coordinates represented by Table 1; atomic coordinates represented by Table 2; atomic coordinates represented by Table 3; atomic coordinates represented by Table 4; and atomic coordinates represented by Table 5;

b. designing a chemical compound using said model; and,

c. chemically synthesizing said chemical compound.

48. A computer-assisted method of structure based drug design of bioactive compounds, comprising:

5 a. providing a model of a three dimensional structure of an Fc receptor (FcR) protein selected from the group consisting of Fc γ RIIa, Fc γ RIIIb and Fc ϵ RI;

b. designing a chemical compound using said model; and,

c. chemically synthesizing said chemical compound.

49. A three dimensional computer image of the three dimensional structure of an FcR protein.

50. The image of Claim 49, wherein said structure substantially conforms with the three dimensional coordinates selected from the group consisting of the three dimensional coordinates listed in Table 1; the three dimensional coordinates listed in Table 2; the three dimensional coordinates listed in Table 3; the three dimensional coordinates listed in Table 4; and the three dimensional coordinates listed in Table 5.

51. The image of Claim 49, wherein said computer image is generated when a set of three dimensional coordinates comprising said three dimensional coordinates are analyzed on a computer using a graphical display software program to create an electronic file of said image and visualizing said electronic file on a computer capable of representing electronic file as a three dimensional image.

52. The image of Claim 49, wherein said three dimensional computer image is represented by a two dimensional image selected from the group consisting of Fig. 4, Fig. 6, Fig. 7, Fig. 8, Fig. 9, Fig. 10, Fig. 14, Fig. 15 and Fig. 16.

53. The image of Claim 49, wherein said three dimensional computer image is used to design a therapeutic compound.

54. A computer-readable medium encoded with a set of
three dimensional coordinates of an FcR protein having a three
dimensional structure that substantially conforms to the
atomic coordinates of Table 1, wherein, using a graphical
5 display software program, said three dimensional coordinates
create an electronic file that can be visualized on a computer
capable of representing said electronic file as a three
dimensional image.

55. A computer-readable medium encoded with a set of
three dimensional coordinates selected from the group
consisting of the three dimensional coordinates represented in
5 Table 1, the three dimensional coordinates represented in
Table 2, the three dimensional coordinates represented in
Table 3, the three dimensional coordinates represented in
Table 4, and the three dimensional coordinates represented in
Table 5, wherein, using a graphical display software program,
said three dimensional coordinates create an electronic file
10 that can be visualized on a computer capable of representing
said electronic file as a three dimensional image.

56. A model of the three dimensional structure of an FcR protein selected from the group consisting of Fc γ RI protein, Fc γ RIIb protein, Fc γ RIIc protein, Fc γ RIIIb protein, Fc ϵ RI protein and Fc α RI protein, said model being produced by the
5 method comprising:

(a) providing an amino acid sequence of an Fc γ RIIa protein and an amino acid sequence of said FcR protein;

10 (b) identifying structurally conserved regions shared between said Fc γ RIIa amino acid sequence and said FcR protein amino acid sequence; and

15 (c) determining atomic coordinates for said FcR protein by assigning said structurally conserved regions of said FcR protein to a three dimensional structure using a three dimensional structure of said Fc γ RIIa protein which substantially conforms to the atomic coordinates represented in Table 1, to derive a model of said three dimensional structure of said FcR protein amino acid sequence.

57. The model of Claim 56, wherein said Fc γ RI protein amino acid sequence comprises SEQ ID NO:7; wherein said Fc γ RIIb protein amino acid sequence comprises SEQ ID NO:5; wherein said Fc γ RIIc protein amino acid sequence comprises SEQ ID NO:6; wherein said Fc γ RIIIb protein amino acid sequence comprises SEQ ID NO:8; wherein said Fc ϵ RI protein amino acid sequence comprises SEQ ID NO:9; and wherein said Fc α RI protein amino acid sequence comprises SEQ ID NO:13.

58. A therapeutic composition that, when administered to an animal, reduces IgG-mediated tissue damage, said therapeutic composition comprising an inhibitory compound that inhibits the activity of an Fc γ receptor (Fc γ R) protein, said 5 inhibitory compound being identified by the method comprising:

10 (a) providing a three dimensional structure of an Fc γ R protein selected from the group consisting of Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIc and Fc γ RIIb, wherein said three dimensional structure of said Fc γ R protein substantially conforms to atomic coordinates represented by Table 1;

15 (b) using said three dimensional structure of said Fc γ R protein to design a chemical compound selected from the group consisting of a compound that inhibits binding of Fc γ R protein to IgG, a compound that substantially mimics the three dimensional structure of Fc γ R protein and a compound that inhibits binding of Fc γ R protein with a molecule that stimulates cellular signal transduction through an Fc γ R protein;

20 (c) chemically synthesizing said chemical compound; and

(d) evaluating the ability of said synthesized chemical compound to reduce IgG-mediated tissue damage.

59. The composition of Claim 58, wherein said IgG-mediated tissue damage results from a biological response selected from the group consisting of IgG-mediated hypersensitivity, IgG-mediated recruitment of inflammatory cells, and IgG-mediated release of inflammatory modulators.

60. The composition of Claim 58, wherein said structure substantially conforms with the atomic coordinates represented in Table 1.

61. The composition of Claim 58, wherein said chemical compound is selected from the group consisting of an inorganic compound and an organic compound.

62. The composition of Claim 58, wherein said chemical compound is selected from the group consisting of oligonucleotides, peptides, peptidomimetic compounds and small organic molecules.

63. The composition of Claim 58, wherein said chemical compound is selected from the group consisting of an analog of said Fc γ R protein, a substrate analog of said Fc γ R protein and a peptidomimetic compound of said Fc γ R protein.

64. The composition of Claim 58, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant, and a carrier.

65. A therapeutic composition that, when administered to an animal, enhances IgG-mediated responses, said therapeutic composition comprising a stimulatory compound that stimulates the activity of an Fc γ receptor (Fc γ R) protein, said stimulatory compound being identified by the method comprising:

(a) providing a three dimensional structure of an Fc γ R protein selected from the group consisting of Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIc and Fc γ RIIb, wherein said three dimensional structure of said Fc γ R protein substantially conforms to atomic coordinates represented by Table 1;

(b) using said three dimensional structure of said Fc γ R protein to design a chemical compound selected from the group consisting of a compound that stimulates binding of Fc γ R protein to IgG, a compound that substantially mimics the three dimensional structure of Fc γ R protein and a compound that stimulates binding of Fc γ R protein with a molecule that stimulates cellular signal transduction through an Fc γ R protein;

(c) chemically synthesizing said chemical compound; and

(d) evaluating the ability of said synthesized chemical compound to enhance IgG-mediated responses.

66. A therapeutic composition that, when administered to an animal, reduces IgE-mediated responses, said therapeutic composition comprising an inhibitory compound that inhibits the activity of an Fc ϵ receptor I (Fc ϵ RI) protein, said inhibitory compound being identified by the method comprising:

(a) providing a three dimensional structure of an Fc ϵ RI protein, wherein said three dimensional structure of said Fc ϵ RI protein substantially conforms to the atomic coordinates selected from the group consisting of the atomic coordinates represented by Table 1, the atomic coordinates represented by Table 2, the atomic coordinates represented by Table 3, the atomic coordinates represented by Table 4 and the atomic coordinates represented by Table 5;

(b) using said three dimensional structure of said Fc ϵ RI protein to design a chemical compound selected from the group consisting of a compound that inhibits binding of Fc ϵ RI protein to IgE, a compound that substantially mimics the three dimensional structure of Fc ϵ RI protein and a compound that inhibits binding of Fc ϵ RI protein with a molecule that stimulates cellular signal transduction through an Fc ϵ RI protein;

(c) chemically synthesizing said chemical compound; and

(d) evaluating the ability of said synthesized chemical compound to reduce IgE-mediated responses.

67. The composition of Claim 66, wherein said IgE-mediated response results from a biological response selected from the group consisting of IgE-mediated hypersensitivity, IgE-mediated recruitment of inflammatory cells, and IgE-mediated release of inflammatory modulators.

68. The composition of Claim 66, wherein said structure comprises the atomic coordinates represented in Table 3.

69. The composition of Claim 66, wherein said structure comprises the atomic coordinates represented in Table 4.

70. The composition of Claim 66, wherein said chemical compound is selected from the group consisting of an inorganic compound and an organic compound.

71. The composition of Claim 66, wherein said chemical compound is selected from the group consisting of oligonucleotides, peptides, peptidomimetic compounds and small organic molecules.

72. The composition of Claim 66, wherein said chemical compound is selected from the group consisting of an analog of said Fc ϵ R protein, a substrate analog of said Fc ϵ RI protein and a peptidomimetic compound of said Fc ϵ RI protein.

73. The composition of Claim 66, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant, and a carrier.

74. A therapeutic composition that, when administered to an animal, enhances IgE-mediated responses, said therapeutic composition comprising a stimulatory compound that stimulates the activity of an Fc ϵ receptor I (Fc ϵ RI) protein, said stimulatory compound being identified by the method comprising:

5 (a) providing a three dimensional structure of an Fc ϵ RI protein, wherein said three dimensional structure of said Fc ϵ RI protein substantially conforms to the atomic coordinates selected from the group consisting of the atomic coordinates represented by Table 1, the atomic coordinates represented by Table 2, the atomic coordinates represented by Table 3, the atomic coordinates represented by Table 4 and the atomic coordinates represented by Table 5;

10 (b) using said three dimensional structure of said Fc ϵ RI protein to design a chemical compound selected from the group consisting of a compound that stimulates binding of Fc ϵ RI protein to IgE, a compound that substantially mimics the three dimensional structure of Fc ϵ RI protein and a compound that stimulates binding of Fc ϵ RI protein with a molecule that stimulates cellular signal transduction through an Fc ϵ RI protein;

15 (c) chemically synthesizing said chemical compound; and

20 (d) evaluating the ability of said synthesized chemical compound to enhance IgE-mediated responses.

75. A method to determine a three dimensional structure of an FcR protein, said method comprising

(a) providing an amino acid sequence of an FcR protein selected from the group consisting of Fc γ RI protein, Fc γ RIIb protein, Fc γ RIIc protein, Fc γ RIIb protein, Fc ϵ RI protein and Fc α RI protein, wherein the three dimensional structure of said FcR protein is not known;

5 (b) analyzing the pattern of folding of said amino acid sequence in a three dimensional conformation by fold recognition; and

10 (c) comparing said pattern of folding of said FcR protein amino acid sequence with the three dimensional structure of Fc γ RIIa protein to determine the three dimensional structure of said FcR protein, wherein said three dimensional structure of said Fc γ RIIa protein substantially 15 conforms to the atomic coordinates represented in Table 1.

76. A method to derive a model of the three dimensional structure of an FcR protein, said method comprising the steps of:

5 (a) providing an amino acid sequence of an FcγRIIa protein and an amino acid sequence of an FcR protein;

(b) identifying structurally conserved regions shared between said FcγRIIa amino acid sequence and said FcR protein amino acid sequence;

10 (c) determining atomic coordinates for said target structure by assigning said structurally conserved regions of said FcR protein to a three dimensional structure using a three dimensional structure of an FcγRIIa protein based on atomic coordinates that substantially conform to the atomic coordinates represented in Table 1 to derive a model of the 15 three dimensional structure of said FcR protein amino acid sequence.

77. The method of Claim 76, further comprising assigning atomic coordinates for side chains of said FcR protein by determining sterically allowable positions using a library of rotamers.

78. A method to derive a three dimensional structure of a crystallized FcR protein, said method comprising the steps of:

5 (a) comparing the Patterson function of a crystallized FcR protein with the Patterson function of crystalline FcγRIIa protein to produce an electron-density map of said crystallized FcR protein; and

10 (b) analyzing said electron-density map to produce said three dimensional structure of said crystallized FcR protein.

79. The method of Claim 78, further comprising the step of electronically simulating said three dimensional structure of said crystallized FcR protein to derive a computer image of said three dimensional structure of said crystallized FcR protein.

5 80. The method of Claim 78, further comprising the step of rotating said Patterson function of said crystallized FcR protein on said Patterson function of said crystalline FcγRIIa protein to determine the correct orientation of said crystallized FcR protein in a crystal of said crystallized FcR protein to identify the initial phases of said crystallized FcR protein.

81. A composition comprising Fc γ RIIa protein in a crystalline form.